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SYSTEMS TO PROMOTE DISSOLUTION OF THROMBI IN THE THORACIC CAVITY

Related Applications

This application is a continuation of copending U.S. Application Serial No.: 09/645,662; Filed August 24, 2000, entitled "Systems and Methods for Enhancing Blood Perfusion Using Ultrasonic Energy," which is incorporated herein by reference.

Field of the Invention

This invention relates to systems and methods for increasing blood perfusion, e.g., in the treatment of myocardial infarction, strokes, and vascular diseases.

Background of the Invention

High frequency (5 mHz to 7 mHz) ultrasound has been widely used for diagnostic purposes. Potential therapeutic uses for ultrasound have also been more recently suggested. For example, it has been suggested that high power, lower frequency ultrasound can be focused upon a blood clot to cause it to break apart and dissolve. The interaction between lower frequency ultrasound in the presence of a thrombolytic agent has also been observed to assist in the breakdown or dissolution of thrombi. The effects of ultrasound upon enhanced blood perfusion have also been observed.

While the therapeutic potential of these uses

for ultrasound has been recognized, their clinical promise has yet to be fully realized. Treatment modalities that can apply ultrasound in a therapeutic way are designed with the premise that they will be operated by trained medical personnel in a conventional fixed-site medical setting. They assume the presence of trained medical personnel in a non-mobile environment, where electrical service is always available. Still, people typically experience the effects of impaired blood perfusion suddenly in public and private settings. These people in need must be transported from the public or private settings to the fixed-site medical facility before ultrasonic treatment modalities can begin. Treatment time (which is often critical in the early stages of impaired blood perfusion) is lost as transportation occurs. Even within the fixed-site medical facility, people undergoing treatment need to be moved from one care unit to another. Ultrasonic treatment modalities must be suspended while the person is moved.

Summary of the Invention

The invention provides systems and methods that make it possible to initiate and maintain treatment of a reduced blood perfusion incident using ultrasound in a clinical location or a non-clinical, even mobile location, outside a traditional medical setting. The systems and methods make effective use of the critical time period before the person reaches a hospital or another traditional medical treatment center. The systems and methods make possible a therapeutic ultrasound treatment modality that "follows the patient" while outside the medical center, while en route to the medical center, and even while being transported within the medical center itself. The systems and methods also make possible in-home therapeutic ultrasound treatment modalities.

Other features and advantages of the inventions are set forth in the following specification and attached drawings.

Brief Description of the Drawings

Fig. 1 is a perspective view of a system for transcutaneously applying ultrasonic energy to affect increased blood perfusion;

Fig. 2 is an enlarged side perspective view of an ultrasonic applicator that forms a part of the system shown in Fig. 1;

Fig. 3 is a side section view, with parts broken away and in section of the applicator shown in Fig. 2;

Fig. 4 is a view of the applicator shown in Fig. 2 held by a stabilization assembly in a secure position overlaying the sternum of a patient, to transcutaneously direct ultrasonic energy toward the vasculature of the heart;

Fig. 5 is a view of the applicator shown in Fig. 2 held by another type of stabilization assembly on the chest of a patient to transcutaneously direct ultrasonic energy toward the vasculature of the heart;

Fig. 6 is a side view of the applicator shown in Fig. 2, in contact with the skin, showing the feature of increasing or decreasing the axial distance between the applicator and the thrombosis site;

Figs. 7A and 7B are side views of the applicator shown in Fig. 2, in contact with the skin, showing the feature of pivoting the application about an axis parallel to the skin;

Fig. 8 is a view of another embodiment of an ultrasonic applicator usable in association with the system shown in Fig. 1, the applicator being shaped to apply ultrasonic energy to the vasculature in the heart without passage through adjacent organs like the lungs,

the system also including an assembly to administer a thrombolytic agent in conjunction with the application of ultrasonic energy;

Fig. 9 is a perspective view of a cooling module and associated heat exchange cassette that the system shown in Fig. 1 can incorporate;

Fig. 10 is a side schematic view of the cooling module and heat exchange cassette shown in Fig. 9;

Fig. 11 is a side schematic view of another embodiment of a cooling module and heat exchange cassette that the system shown in Fig. 1 can incorporate; and

Fig. 12 is a plan view of a kit, in which all or some of the disposable components of the system shown in Fig. 1 can be packaged before use, along with instructions for using the components to achieve the features of the invention.

The invention may be embodied in several forms without departing from its spirit or essential characteristics. The scope of the invention is defined in the appended claims, rather than in the specific description preceding them. All embodiments that fall within the meaning and range of equivalency of the claims are therefore intended to be embraced by the claims.

Description of the Preferred Embodiments

The various aspects of the invention will be described in connection with the therapeutic indication of providing increased blood perfusion by the transcutaneous application of ultrasonic energy. That is because the features and advantages of the invention are well suited to this therapeutic indication. Still, it should be appreciated that many aspects of the invention can be applied to achieve other diagnostic or therapeutic objectives as well.

Furthermore, in describing the various aspects of the invention in the context of the illustrated

embodiment, the region targeted for an increase in blood perfusion is the thoracic cavity (i.e., the space where the heart and lungs are contained). It should be appreciated, however, that the features of invention have application in other regions of the body, too, for example, in the arms, legs, or brain.

I. System for Providing Noninvasive Ultrasound-Assisted Blood Perfusion

Fig. 1 schematically shows a compact, portable therapeutic system 10 that makes it possible to treat a person who needs or who is likely to need an increase in the flow rate or perfusion of circulating blood.

The system 10 includes durable and disposable equipment and materials necessary to treat the person at a designated treatment location. In use, the system 10 affects increased blood perfusion by transcutaneously applying ultrasonic energy.

As Fig. 1 shows, the system 10 includes at the treatment location an ultrasound generating machine 16. The system 10 also includes at the treatment location at least one ultrasound applicator 18, which is coupled to the machine 16 during use. As Figs. 4 and 5 show, the system 10 also includes an assembly 12 for use with the applicator 18 to stabilize the position of the applicator 18 on a patient for hands-free use. In the illustrated embodiment (see Figs. 4 and 5), the applicator 18 is secured against movement on a person's chest, overlaying the sternum, to direct ultrasonic energy toward the vasculature of the heart.

The location where treatment occurs can vary. It can be a traditional clinical setting, where support and assistance by one or more medically trained care givers are immediately available to the person, such as inside a hospital, e.g., in an emergency room, catheter lab, operating room, or critical care unit. However, due to

the purposeful design of the system 10, the location need not be confined to a traditional clinical setting. The location can comprise a mobile setting, such as an ambulance, helicopter, airplane, or like vehicle used to convey the person to a hospital or another clinical treatment center. The location can even comprise an everyday, public setting, such as on a cruise ship, or at a sports stadium or airport, or a private setting, such as in a person's home, where the effects of low blood perfusion can arise.

By purposeful design of durable and disposable equipment, the system 10 can make it possible to initiate treatment of a reduced blood perfusion incident in a non-clinical, even mobile location, outside a traditional medical setting. The system thereby makes effective use of the critical time period before the person enters a hospital or another traditional medical treatment center.

The features and operation of the system 10 will now be described in greater detail.

A. The Ultrasound Generator

Fig. 1 shows a representative embodiment of a machine 16. The machine 16 can also be called an "ultrasound generator." The machine 16 is intended to be a durable item capable of long term, maintenance free use.

As shown in Fig. 1, the machine 16 can be variously sized and shaped to present a lightweight and portable unit, presenting a compact footprint suited for transport, e.g., mounted on a conventional pole stand 14, as Fig. 1 shows. This allows the machine 16 to accompany the patient from one location to another. The machine 16 can alternatively be sized and shaped to be mounted at bedside, or to be placed on a table top or otherwise occupy a relatively small surface area. This allows the machine 16 to travel with the patient within an

ambulance, airplane, helicopter, or other transport vehicle where space is at a premium. This also makes possible the placement of the machine 16 in a non-obtrusive way within a private home setting, such as for the treatment of chronic angina.

In the illustrated embodiment, the machine 16 includes a chassis 22, which can be made of molded plastic or metal or both. The chassis houses a module 24 for generating electric signals. The signals are conveyed to the applicator 18 by an interconnect 30 to be transformed into ultrasonic energy. A controller 26, also housed within the chassis 22 (but which could be external of the chassis 22, if desired), is coupled to the module 24 to govern the operation of the module 24. Further details regarding the controller 26 will be described later.

The machine 16 also preferably includes an operator interface 28. Using the interface 28, the operator inputs information to the controller 26 to affect the operating mode of the module 24. Through the interface 28, the controller 26 also outputs status information for viewing by the operator. The interface 28 can provide a visual readout, printer output, or an electronic copy of selected information regarding the treatment. The interface 28 is shown as being carried on the chassis 22, but it could be located external of the chassis 22 as well. Further details regarding the interface 28 will be described later.

The machine 16 includes a power cord 30 for coupling to a conventional electrical outlet, to provide operating power the machine 16. The machine 16 also preferably includes a battery module 34 housed within the chassis 22, which enables use of the machine 16 in the absence or interruption of electrical service. The battery module 34 can comprise rechargeable batteries, that can be built in

the chassis 22 or, alternatively, be removed from the chassis 22 for recharge. Likewise, the battery module 34 can include a built-in or removable battery recharger 36. Alternatively, the battery module 34 can comprise disposable batteries, which can be removed for replacement.

Power for the machine 16 can also be supplied by an external battery and/or line power module outside the chassis 22. The battery and/or line power module is releasably coupled at time of use to the components within the chassis 22, e.g., via a power distribution module within the chassis 22.

The provision of battery power for the machine 16 frees the machine 16 from the confines surrounding use of conventional ultrasound equipment, caused by their dependency upon electrical service. This feature makes it possible for the machine 16 to provide a treatment modality that continuously "follows the patient," as the patient is being transported inside a patient transport vehicle, or as the patient is being shuttled between different locations within a treatment facility, e.g., from the emergency room to a holding area within or outside the emergency room.

In a representative embodiment, the chassis 22 measures about 12 inches x about 8 inches x about 8 inches and weighs about 9 pounds.

B. The Ultrasound Applicator

As best shown in Figs. 2 and 3, the applicator 18 can also be called the "patient interface." The applicator 18 comprises the link between the machine 16 and the treatment site within the thoracic cavity of the person undergoing treatment. The applicator 18 converts electrical signals from the machine 16 to ultrasonic energy, and further directs the ultrasonic energy to the targeted treatment site.

Desirably, the applicator 18 is intended to be a disposable item. At least one applicator 18 is coupled to the machine 16 via the interconnect 30 at the beginning a treatment session. The applicator 18 is preferably decoupled from the interconnect 30 (as Fig. 2 shows) and discarded upon the completing the treatment session. However, if desired, the applicator 18 can be designed to accommodate more than a single use.

As Figs. 2 and 3 show, the ultrasound applicator 18 includes a shaped metal or plastic body 38 ergonomically sized to be comfortably grasped and manipulated in one hand. The body 38 houses at least one ultrasound transducer 40 (see Fig. 3).

The body 38 can include a heat sink region 42 placed about the transducer 40, to conduct heat generated by the transducer or transducers during operation, to minimize heating effects. As will be described later, impedance matching or active cooling can also be achieved to prevent or counter heating effects.

Preferably, the plastic body 38 includes a stand-off region 44 or skirt extending from the front mass or face 46 of the transducer 40. The skirt region 44 spaces the transducer face 46 a set distance from the patient's skin. The skirt region 44 prevents direct contact between the transducer face 46 and the person's skin.

Desirably, an ultrasonic conductive material 48 overlays the skirt region 44, to serve as the ultrasonic radiation region for contact with the person's skin. The material 48 can be formed, e.g., from a hydrophilic material or other composition that has minimal acoustic attenuation. In a preferred arrangement, the skirt region 44 forms an area for the ultrasonic radiation region (which the material 48 covers) that is larger than the area of the front mass or face 46 of the transducer 40. In a preferred embodiment, the front mass 46 of the

transducer 40 measures about 2 inches in diameter, whereas the radiation region formed by the skirt region 44 measures about 4 inches in diameter. An applicator 18 that presents a radiation region of significantly larger diameter than the front mass of the transducer 40 (e.g., in a ratio of at least 2:1)reduces overall weight and makes possible an ergonomic geometry (like that shown in Fig. 2) that enables single-handed manipulation during set-up, even in confined quarters, and further provides(with the assembly 12) hands-free stability during use. In a representative embodiment, the applicator 18 measures about 4 inches in diameter about the skirt region 44, about 4 inches in height, and weighs about one pound.

The material 48 defines a bladder chamber 50 between it and the transducer face 46. The bladder chamber 50 accommodates a volume of liquid or gel that is also conductive to ultrasonic energy, to further cushion the contact between the applicator 18 and the skin.

As will be described later, liquid may be circulated through ports 52 (see Fig. 3) into and out of the bladder chamber 50, to conduct heat from the bladder chamber 50. As will also be described later, the volume of fluid occupying the bladder chamber 50 can be varied, if desired, to distend the material 48 to accommodate different skin contours and promote even distribution of ultrasonic energy during use.

The interconnect 30 carries a distal connector 54 (see Fig. 2), designed to easily plug into a mating outlet 56 in the transducer 40. A proximal connector 58 on the interconnect 30 likewise easily plugs into a mating outlet 60 on the chassis 22 (see Fig. 1), which is itself coupled to the controller 26. In this way, the applicator 18 can be quickly connected to the machine 16 at time of use, and likewise quickly disconnected for

discard once the treatment session is over. Other quick-connect coupling mechanisms can be used.

As Fig. 4 shows, a stabilization assembly 12 allows the operator to temporarily but securely mount the applicator 18 against an exterior skin surface for use. In the illustrated embodiment, since the treatment site exists in the thoracic cavity, the attachment assembly 54 is fashioned to secure the applicator 18 on the person's chest, overlaying the sternum or breastbone, as Fig. 4 shows.

Just as the applicator 18 can be quickly coupled to the machine 16 at time of use, the stabilization assembly 12 also preferably makes the task of securing and removing the applicator 18 on the patient simple and intuitive. Thus, the stabilization assembly 12 makes it possible to secure the applicator 18 quickly and accurately in position on the patient in cramped quarters or while the person (and the system 10 itself) is in transit.

The stabilization assembly 12 can be variously constructed. In the embodiment shown in Fig. 4, the stabilization assembly 12 comprises a sling 62 worn on the back of the patient between the waist and shoulders. The sling 62 carries a shoulder loop 64 and a waist loop 66. The loops 64 and 66 are made of a stretchable, elastic material. The loops 64 and 66 can be stretched to hook into flanges 68 formed on the body 38 of the applicator 18 (also shown in Fig. 2). The stretchable loops 64 and 66 allow for a rapid mounting and removal of the applicator 18 on the chest of the patient. The stretchable loops 64 and 66 also securely hold the applicator 18 in a stable position on the patient, even in the midst of a dynamic and mobile environment.

As Fig. 4 shows, the stabilization assembly 12 preferably occupies only a relatively small area on the

chest. The stabilization assembly 12 (and the compact size of the applicator 18 itself) allow other treatment devices, e.g., a twelve lead ECG, to be placed on the chest at the same time the applicator 18 is being used.

In another embodiment (see Fig. 5), the stabilization assembly 12 comprises halter straps 70 and 72 worn about the chest and shoulders of the patient. The straps 70 and 72 are made of quick release material, e.g., from Velcro™ material. The straps can be easily passed through rings 74 formed in the body 38 of the applicator 18, and doubled back upon themselves to be secured together. This arrangement, like the arrangement shown in Fig. 4, allows for rapid placement and removal of the applicator 18 on the chest (sternum) of the patient. Also, like the stabilization assembly 12 shown in Fig. 4, the assembly 12 shown in Fig. 5 also does not to impede the placement of other treatment devices on the chest simultaneously with the applicator 18.

For added comfort in either embodiment of the stabilization assembly 12, the sling 62 or halter strips 70/72 can be attached to a flexible back piece (not shown) worn on the patient's back. The back piece can comprise, e.g., a flexible cloth or plastic sheet or pad, formed in the manner of the back half of a vest. The slings 62 or halter straps 70/72 are sown or buckled to the back piece and extend forward about the shoulders and chest of the patient, to be coupled to the applicator 18 in the fashion shown Figs. 4 and 6 show. The sling 62 or halter straps 70/72 transfer the weight of the applicator 18 to the back piece. The back piece distributes the weight borne by the sling 62 or halter straps 70/72 in a uniform manner across the patient's back.

In the illustrated embodiment (see Figs. 6, 7A and 7B), the applicator 18 can include a mechanism for

adjusting the orientation of at least one transducer 40 relative to the treatment site. The mechanism can, e.g., adjust the axial distance between the transducer 40 and the treatment site (see Fig. 6) by changing the volume of fluid residing within the bladder chamber 50. This raises or lowers the transducer 40 on the skin surface and, respectively, increases or decreases the axial distance between the face 46 of the transducer 40 and the treatment site. The changeable volume also makes it possible to adjust the applicator 18 to conform to different skin contours of the patient.

Additionally, or in combination, the bladder chamber 50 can include, e.g., isolated interior compartments 76 (see Figs. 7A and 7B), so that the volume of fluid can be differentially adjusted the compartments 64, to pivot the face 46 of the transducer 40 either clockwise or counterclockwise about an axis A parallel to the skin. In this way, as Figs. 7A and 7B show, the angle of the transducer 40 relative to the treatment site can be adjusted.

If desired (see Fig. 6), an external ultrasound conducting material 78 can also be applied directly to the skin of the person, to form an ultrasound conducting interface between the applicator 18 and the treatment site. The external material 78 can comprise, e.g., a gel material (such as AQUASONIC® 100, by Parker Laboratories, Inc., Fairfield, N.J.). The external material 78 can possess sticky or tacky properties, to further enhance the securement of the applicator 18 to the skin.

The applicator 18 can be formed in various shapes for ease of storage, handling, and use. As Figs. 2 and 3 show, the applicator 18 can comprise generally discus or hockey puck shape. As Fig. 8 shows, the applicator 18 can be shaped in a more elliptical or elongated fashion that aligns with the axis of the sternum. In this

arrangement, passage of ultrasonic energy into adjacent organs, e.g., the lungs, is minimized.

C. Using a Thrombolytic Agent

As Fig. 8 shows, the system 10 can further include at the treatment location a delivery system 32 for introducing a thrombolytic agent 20 in conjunction with the use of the applicator 18 and machine 16. In this arrangement, the effect of increased blood perfusion caused by the application of ultrasonic energy can also be enhanced by the thrombolytic effect of the agent 20.

Preferably, the thrombolytic agent 20 is introduced into a thrombosis site (using the delivery system 32), prior to, in conjunction with, or after the application of ultrasound. The interaction between the applied ultrasound and the thrombolytic agent 20 is observed to assist in the break-down or dissolution of the thrombi, compared with the use of the thrombolytic agent 20 in the absence of ultrasound. This phenomenon is discussed, e.g., in Carter United States Patent 5,509,896; Siegel et al United States Patent 5,695,460; and Lauer et al United States Patent 5,399,158, which are each incorporated herein by reference.

The process by which thrombolysis is affected by use of ultrasound in conjunction with a thrombolytic agent 20 can vary according to the frequency, power, and type of ultrasonic energy applied, as well as the type and dosage of the thrombolytic agent 20. The application of ultrasound has been shown to cause reversible changes to the fibrin structure within the thrombus, increased fluid dispersion into the thrombus, and facilitated enzyme kinetics. These mechanical effects beneficially enhance the rate of dissolution of thrombi. In addition, cavitational disruption and heating/streaming effects can also assist in the breakdown and dissolution of thrombi.

The type of thrombolytic agent 20 used can vary. The

thrombolytic agent 20 can comprise a drug known to have a thrombolytic effect, such as t-PA, TNKase, or RETAVASE. Alternatively (or in combination), the thrombolytic agent 20 can comprise an anticoagulant, such as heparin; or an antiplatelet drug, such as a GP IIb IIIa; or a fibrinolytic drug; or a non-prescription agent having a known beneficial effect, such as aspirin. Alternatively (or in combination), the thrombolytic agent 20 can comprise microbubbles, which can be ultrasonically activated; or microparticles, which can contain albumin.

The thrombolytic syndrome being treated can also vary, according to the region of the body. For example, in the thoracic cavity, the thrombolytic syndrome can comprise acute myocardial infarction, or acute coronary syndrome. The thrombolytic syndrome can alternatively comprise suspect myocardial ischemia, prinzmetal angina, chronic angina, or pulmonary embolism.

The thrombolytic agent 20 is typically administered by the delivery system 32 intravenously prior to or during the application of ultrasonic energy. The dosage of the thrombolytic agent 20 is determined by the physician according to established treatment protocols.

It may be possible to reduce the typical dose of thrombolytic agent 20 when ultrasonic energy is also applied. The ability to reduce the dosage of thrombolytic agent 20, when ultrasound is also applied, can lead to additional benefits, such as decreased complication rate, an increased patient population eligible for the treatment, and increased locations where the treatment can be administered (i.e., outside hospitals and critical care settings, such as in ambulances, helicopters, other public settings, as well as in private, in-home settings).

D. Other Treatment Applications

The system 10 can be used to carry out non-

thrombolytic therapeutic treatment objectives, as well.

For example, the system 10 can be used to carry out cardiac rehabilitation. The repeated application of ultrasound over an extended treatment period can exercise and strengthen heart muscle weakened by disease or damage. As another example, treatment using ultrasound can stimulate additional capillary or microcirculatory activity, resulting in an angiogenesis effect. As an additional example, treatment using ultrasound can facilitate an improvement in heart wall motion or function

The purposeful design of the durable and disposable equipment of the system 10 makes it possible to carry out these therapeutic protocols outside a traditional medical setting, such as in a person's home.

E. Exemplary Treatment Modalities

As is apparent, the system 10 can accommodate diverse modalities to achieve desired treatment protocols and outcomes. These modalities, once identified, can be preprogrammed for implementation by the controller 26.

1. Controlling Output Frequency

Depending upon the treatment parameters and outcome desired, the controller 26 can operate a given transducer 40 at a fundamental frequency below about 50 kHz, or in a fundamental frequency range between about 50 kHz and about 1 MHz, or at fundamental frequencies above 1 MHz.

A given transducer 40 can be operated in either a pulsed or a continuous mode, or in a hybrid mode where both pulsed and continuous operation occurs in a determined or random sequence at one or more fundamental frequencies.

The applicator 18 can include multiple transducers 40 (or multiple applicators 18 can be employed simultaneously for the same effect), which can be individually conditioned by the controller 26 for

operation in either pulsed or continuous mode, or both. For example, the multiple transducers 40 can all be conditioned by the controller 26 for pulsed mode operation, either individually or in overlapping synchrony. Alternatively, the multiple transducers 40 can all be conditioned by the controller 26 for continuous mode operation, either individually or in overlapping synchrony. Still alternatively, the multiple transducers 40 can be conditioned by the controller 26 for both pulsed and continuous mode operation, either individually or in overlapping synchrony.

One or more transducers 40 within an array of transducers 40 can also be operated at different fundamental frequencies. For example, one or more transducers 40 can be operated at about 25 kHz, while another one or more transducers 40 can be operated at about 100 kHz. More than two different fundamental frequencies can be used, e.g., about 25 kHz, about 50 kHz, and about 100 kHz.

Operation at different fundamental frequencies provides different effects. For example, given the same power level, at about 25 kHz, more cavitation effects are observed to dominate; while at 100 kHz, more mechanical effects are observed to dominate; and while above 500 kHz, more heating effects are observed to dominate.

The controller 26 can trigger the fundamental frequency output according to time or a physiological event (such as ECG or respiration).

2. Controlling Output Power Parameters

Also depending upon the treatment parameters and outcome desired, the controller 26 can operate a given transducer 40 at a prescribed power level, which can remain fixed or can be varied during the treatment session. The controller 26 can also operate one or more transducers 40 within an array of transducers 40 (or when

using multiple applicators 18) at different power levels, which can remain fixed or themselves vary over time. Power level adjustments can be made without fundamental frequency adjustments, or in combination with fundamental frequency adjustments.

The parameters affecting power output take into account the output of the signal generator module 24; the physical dimensions and construction of the applicator 18; and the physiology of the tissue region to which ultrasonic energy is being applied. In the context of the illustrated embodiment, these parameters include the total output power (P_{Total}) (expressed in watts -- W) provided to the transducer 40 by the signal generator module 24; the density of the power ($P_{Density}$) (expressed in watts per square centimeter -- W/cm^2) applied by the ultrasound radiating area of the applicator 18, which takes into account the total power P_{Total} and the area of the material 48 overlaying the skirt 44; and the peak rarefactional acoustic pressure ($P_{Peak(Neg)}$) (expressed in Pascals -- Pa) that the tissue experiences, which takes into consideration that the physiological tolerance of animal tissue to rarefactional pressure conditions is much less than its tolerance to compressional pressure conditions. Generally, it is believed that the peak rarefactional acoustic pressure applied to animal tissue should not exceed about 175 kPa. $P_{Peak(Neg)}$ can be derived as a known function of W/cm^2.

In a preferred embodiment, the applicator 18 is sized to provide a power density equal to or less than 2 W/cm^2 at a maximum total power output of equal to or less than 200 W (most preferably $50W \leq P_{Total} \leq 150$ W) operating at a fundamental frequency of less than or equal to 500 kHz. Ultrasonic energy within the range of fundamental frequencies specified passes through bone, while also providing selectively different cavitational and

mechanical effects (depending upon the frequency), and without substantial heating effects, as previously described. Power supplied within the total power output range specified meets the size, capacity, and cost requirements of battery power, to make a transportable, "follow the patient" treatment modality possible, as already described. Power density supplied within the power density range specified keeps peak rarefactional acoustic pressure within physiologically tolerable levels. The applicator 18 meeting these characteristics can therefore be beneficially used in conjunction with the transportable ultrasound generator machine 16, as described.

As stated above, the controller 26 can trigger the output according to time or a physiological event (such as ECG or respiration).

3. Cooling

The controller 26 can also include a cooling function. During this function, the controller 26 causes a liquid (e.g., water or saline or another fluid) to circulate at or near the ultrasound applicator 18. The circulation of liquid conducts heat that may arise during the formation and application of ultrasonic energy.

In one embodiment, the machine 16 carries out this function using a fluid handling module 80 on the machine 16 (see Fig. 9). The module 80 operatively engages a pumping and heat exchange cassette 84 coupled to the applicator 18.

In the embodiment shown in Fig. 9, the module 80 is physically located within a cavity 82 formed in the machine 16. Access to the cavity 82 is governed by a hinged door 120 (shown closed in Fig. 1 and opened in Fig. 9). The cassette 84 is received in the cavity 82 when the door 120 is opened and enclosed within the cavity 82 for use when the door 120 is subsequently

closed. Opening the door 120 after use allows the operator to remove and dispose of the cassette 84.

Alternatively, the cavity 82 can be free of a closure door 120, and the cassette 82 directly plugs into the cavity 82. In this arrangement, the top surface of the cassette 84 serves as a closure lid.

In the illustrated embodiment (see Fig. 9), the cassette 84 comprises a molded plastic assembly that is integrally connected by tubing 86 to the applicator 18. In this arrangement, the cassette 84 forms a pre-connected unit of the disposable components of the system 10. Alternatively, the cassette 84 and tubing 86 could form a separate component that is connected to the applicator 18 at time of use. In this arrangement, the cassette 84 and tubing 86 still preferably comprise a single use, disposable unit.

In the illustrated embodiment, the tubing 86 includes two fluid flow lumens 88 and 90 (although individual tubing lengths can also be used). In the embodiment shown in Fig. 9, the cassette 84 includes an internal pumping mechanism 92, such as a diaphragm pump or centrifugal pump. Fig. 10 also diagrammatically shows this arrangement.

The cassette 84 also includes an internal heat exchange circuit 94 coupled to the pumping mechanism 92. The pumping mechanism 92, when operated, circulates fluid through the lumens 88 and 90 and the heat exchange circuit 94. Fluid is thereby circulated by the pumping mechanism 92 in a closed loop from the cassette 84 through the lumen 88 and into the bladder chamber 50 of the applicator 18 (through one of the ports 52), where heat generated by operation of the transducer 40 is conducted into the fluid. The heated fluid is withdrawn by the pumping mechanism 92 from the bladder chamber 50 through the other lumen 90 (through the other port 52)

into the cassette 84. Preformed interior fluid paths in the cassette 84 direct the fluid through the heat exchange circuit 94, where heat is conducted from the fluid.

The circulating fluid can be supplied by a bag 96 that is coupled to the tubing 86 at time of use or, alternatively, that is integrally connected to the cassette during manufacture. Still alternatively, the fluid channels of the cassette 84 and the tubing 86 can be charged with fluid during manufacture.

In this arrangement (see, in particular, Fig. 10), the module 80 includes an internal electric motor 98 having a drive shaft 100. The motor drive shaft 100 is keyed to operatively engage the driver 108 of the pumping mechanism 92 when the cassette 84 is fitted into the cavity 82. Operation of the motor 98 drives the pumping mechanism 92 to circulate fluid to cool the applicator 18.

Also in the illustrated embodiment (see Fig. 10), the cassette 84 includes an externally exposed heat conducting plate 102. The plate 102 is coupled in heat conducting association with the heat exchange circuit 94. When the cassette 84 is fitted within the cavity 82 of the module 80, the heat conducting plate 102 on the cassette 84 contacts a heat conducting plate 104 in the module 80. The plate 104 is cooled by an interior fan 106 in the module 80, to withdraw heat from the heat exchange circuit 94 of the cassette 84. In this way, fluid is cooled as it circulates through the cassette.

In the embodiment shown in Fig. 10, no fluid circulates within the module 80 itself. The closed loop flow of fluid is all external to the machine 16.

In an alternative arrangement (see Fig.11), the cassette 84 does not include an on-board pumping mechanism. Instead, the module 80 includes an interior

pump 110 that couples to ports 112 that communicate with the interior fluid paths of the cassette 84. In this arrangement, the pump 110 conveys fluid into and through the module 84 to circulate fluid through the heat exchanger circuit 94 of the cassette 84 in the manner previously described.

Other arrangements are also possible. For example, the cooling function can be implemented by conventional peristaltic pump head mounted outside the chassis 22. The pump head couples to external tubing coupled to the applicator 18 to circulate fluid through the cassette. Still alternatively, the fluid handling module 80 can comprise a separate unit that can be remotely coupled to the machine 16 when cooling is desired.

Alternatively, the cassette can communicate with a separate bladder placed about the applicator 18 to achieve localized cooling.

The cooling function can be obviated by the controller 26 by transducer 40 impedance matching.

4. Monitoring and Displaying Output

The controller 26 can implement various output monitoring and feedback control schemes. For example, the controller 26 can monitor ultrasonic output by employing one or more accelerometers 78 (see Fig. 3) (or other types of displacement or compression feedback components) on or within the applicator 18. The ultrasonic output that is monitored in this way can comprise fundamental frequency, total power output, power density, acoustic pressure, or Mechanical Index (MI). The controller 26 can also monitor temperature conditions using one or more temperature sensors 140 or thermistors on the applicator 18.

Implementing feedback control schemes, the controller 26 can also execute various auto-calibration schemes. The controller 26 can also implement feedback

control to achieve various auto-optimization schemes, e.g., in which power, fundamental frequency, and/or acoustic pressure outputs are monitored and optimized according to prescribed criteria to meet the desired treatment objectives and outcomes.

The controller 26 can also implement schemes to identify the nature and type of applicator when coupled to the machine. These schemes can also include functions that register and identify applicators that have undergone a prior use, to monitor and, if desired, prevent reuse, store treatment data, and provide serial number identification. This function can be accomplished using, e.g., analog electrical elements (e.g., a capacitor or resistor) and/or solid state elements (micro-chip, ROM, EEROM, EPROM, or non volatile RAM) within the applicator 18 and/or in the controller 26.

The controller 26 can also display the output in various text or graphical fields on the operator interface 28. For example, the controller 26 can conveniently display on the interface a timer, showing the time of treatment; a power ON indicator; a cooling ON indicator; and ultrasonics ON indicator; and other data reflecting information helpful to the operator, for example, the temperature, fundamental frequency, the total power output, the power density, the acoustic pressure, and/or Mechanical Index.

The controller 26 can also include an internal or external input device to allow the operator to input information (e.g., the patient's name and other identification) pertaining to the treatment session. The controller 26 can also include an internal or external storage device to allow storage of this information for output to a disk or a printer in a desired format, e.g., along with operating parameters such as acoustical intensity, treatment duration, etc.

The controller 26 can also provide the means to link the machine 16 at the treatment location in communication with one or more remote locations via, e.g., cellular networks, digital networks, modem, Internet, or satellites.

5. Integrated Function

The machine 16 and associated applicator 18 can form a part of a free standing system 10, as the previous drawings demonstrate. The machine 16 can also be integrated into another functional device, such as an ECG apparatus, a defibrillator apparatus, a diagnostic ultrasound apparatus, or another other diagnostic or therapeutic apparatus. In this arrangement, the former functionality of the diagnostic or therapeutic device is augmented by the added ability to provide noninvasive ultrasound-induced increased blood perfusion and/or thrombolysis.

E. Supplying the System

As before explained, the machine 16 is intended to be a durable item capable of multiple uses.

One or more of the disposable components of the system 10, which are intended for single use, can be separately supplied in a kit 114. For example, in one embodiment (see Fig. 12), the kit 114 can include, contained within in a sealed, tear-apart package 116, the applicator 18 and instructions 118 for using the applicator 18 in association with the machine 16 to transcutaneously apply ultrasonic energy to enhance blood perfusion. In this regard, the instructions 118 may set forth all or some of the method steps, described above. The instructions 118 may also comprise the method steps to transcutaneously apply ultrasonic energy in association with the administration of a thrombolytic agent.

Additional elements may also be provided with the

applicator 18 in the kit 114, such as the patient stabilization assembly 12, the heat exchanging cassette 84 and associated tubing 86, and exterior ultrasound conducting material 78. These and other additional elements may also be packaged separately.

The instructions 118 can comprise printed materials. Alternatively, the instructions 118 can comprise a recorded disk or media containing computer readable data or images, a video tape, a sound recording, and like material.

Various features of the invention are set forth in the following claims.